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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/593,811 | 01/18/2007 | Kiyoshi Okamoto | 296514US0PCT | 5613 |

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| EXAMINER | |
|---|---|
| HAMA, JOANNE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 08/07/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/593,811 | OKAMOTO ET AL. | |
| | Examiner | Art Unit | |
| | JOANNE HAMA | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *13,14,24-30 and 40-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-23 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/22/06,12/22/06,3/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group 1 in the reply filed on May 9, 2008 is acknowledged. The traversal is on the ground(s) that the restriction is proper if the claims of the restricted groups are independent or patentably distinct (Applicant's response, page 2). Applicant indicates that the instant application is directed to measuring the transcriptional activity of cell transplanted into non-human animals (Applicant's response, page 3). In response, the Examiner has reconsidered the restriction and rejoins the methods of Groups 1-3 because the three methods are not patentably distinct from each other.

The requirement is still deemed proper and is therefore made FINAL.

With regard to the species election, Applicant elected SEQ ID NO. 1 without traverse.

Claims 13, 14, 24-30, 40-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 9, 2008.

Claims 1-12, 15-23, 31-39, drawn to measuring transcriptional activity, number of cells, and measuring tumor volume in cells transplanted in a non-human animal, are under consideration.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Information Disclosure Statement***

Applicant filed Information Disclosure Statements on September 22, 2006, December 22, 2006, and March 26, 2008. The IDSes have been considered.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 9, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Suarez-Pinzon et al., 2002, Cell Transplantation, 11: 519-528, previously cited, see 892 filed April 9, 2008, as evidenced by Sime et al., 1997, The Journal of Clinical Investigation, 100: 768-776.

Suarez-Pinzon et al. teach islet cells transfected with construct were transplanted into diabetic NOD mice. Blood glucose levels in NOD mice transplanted with islets comprising an adenoviral vector comprising the coding sequence of TGF-beta1 exhibited low blood glucose levels for a longer period of time than mice comprising islets transfected with empty adenoviral vector or non-

transfected islet (Suarez-Pinzon et al., page 522, 1st col. under "Effects of TGF-beta1 Overexpression by Islet Grafts in NOD Mice", see also Figure 3).

With regard to the claims being drawn to a "transcription regulatory sequence" (claim 2), Suarez-Pinzon teach that the TGF-beta1 adenoviral constructs were obtained from Dr. Jack Gauldie, who published the vector in the publication by Sime et al., 1997. In making the vector, the vector comprised a CMV promoter (Sime et al., page 769, 1st col., under "Construction of recombinant adenoviruses").

With regard to the claims being drawn to the protein being a "secretory enzyme" (claim 4), Suarez-Pinzon et al. teach that TGF-beta1 secreted in cell culture media can be measured (Suarez-Pinzon et al., page 521, 2nd col. under "Expression and Secretion of TGF-beta1 in Transfected Islets").

With regard to the claims being drawn to measuring the amount of secretory protein in blood by measuring enzymatic activity (claims 9, 10), Suarez-Pinzon et al. teach that blood glucose levels were measured (Suarez-Pinzon et al., Figure 3).

Thus, the claims are rejected.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, 15-23, 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dachs et al., 1997, Nature Medicine, 3: 515-520, in view of Shibata et al., 2000, Gene Therapy, 7: 493-498, Schneider et al., US Patent 6,420,338 B1, patented July 16, 2002, Shibata et al., 1998, Int. J. Radiation Oncology Biol. Phys. 42: 913-916, Liu et al., 1995, Circulation Research 77: 683-643 (printout of 30 pages), Dirks et al. US Patent 6,060,273, patented May 9, 2000, Ciccarone et al., US Patent 5,932,590, patented August 3, 1999.

Dachs et al. teach that hypoxia can induce activity of a hypoxia responsive element (HRE) from mouse phosphoglycerate kinase-1 (PGK-1). An expression construct comprising the HRE induced expression of a reporter gene ("CD2") in hypoxic regions of tumors transplanted in nude mice (Dachs et al., page 516, 2nd col., under "Hypoxia induces marker gene expression in vivo"). Dachs et al. teach that the use of the HRE has applications in gene therapy of cancer, as the HRE can be used to specifically express a therapeutic gene in cancer cells. For example, Dachs et al. teach that when using their HRE construct, expression of cytosine deaminase sensitizes cancer cells to chemotherapeutic agent, 5-fluorocytosine (Dachs et al., page 516).

While Dachs et al. teach the use of a HRE from PGK-1, they do not teach that the HRE was from vascular endothelial growth factor (VEGF).

Shibata et al. teach vascular endothelial growth factor (VEGF) is upregulated by hypoxia and such regulatory mechanism can enable an artisan to achieve hypoxia-inducible expression of therapeutic genes (Shibata et al.,

abstract). Shibata et al. teach that constructs with five copies of hypoxia-responsive elements derived from the 5' untranslated region (UTR) of human VEGF showed transcriptional activation at low oxygen tension relevant to tumor hypoxia (Shibata et al., abstract, also page 493, 2nd col., 1st parag.).

Because Dachs et al. and Shibata et al. teach methods of gene therapy cancer treatment using HREs, it would have been obvious to one skilled in the art to substitute the HRE taught by Dachs et al. with that of Shibata et al. to achieve the predictable result of expressing a gene of interest in solid tumors.

While Dachs et al. teach the use of CD2 as a reporter gene, they do not teach the use of secretory alkaline phophatase.

Schneider et al. teach that placental alkaline phosphatase is useful as a reporter gene because the enzyme is secreted from the cell and the level of reporter gene expression can be measured from blood or a tissue sample. Alkaline phosphatase activity can be measured by calometric, bioluminescent or chemiluminescent assays (Schneider et al., col. 25, 2nd parag.). These teachings would address the limitations of instant claims 4, 5, 7, 9, 10, 11, 16, 17, 19, 21-23, 32, 33, 35, 37-39. Because both Dachs et al. and Schneider et al. teach methods of measuring gene expression, it would have been obvious to substitute Dachs et al.'s CD2 with that of alkaline phosphatse to achieve the predictable result of measuring gene expression driven by a promoter. It is noted that an artisan would want to measure reporter gene expression during cancer treatment because the amount of gene expression driven by a cancer cell would give an

artisan insight as to changes in number of cancer cells or changes in cancer cell activity.

With regard to the claims being drawn to the use of SEQ ID NO. 1 (e.g. claim 3) Shibata et al. teach that their expression construct, comprising 5 copies of the HRE, operably linked to a minimal E1b promoter was made in reference 7, Shibata et al., 1998. who refer to reference 10, Liu et al., 1995. Liu et al., teach consensus sequence found in the VEGF hypoxia response element that is highly homologous to the HIF-1 recognition sequence (Liu et al., Figure 4, sequence "A-G")). SEQ ID NO. 1 is nested within Liu et al.'s sequence.

With regard to the claims being drawn to the use of secretory placenta-derived alkaline phosphatase (SEQ ID NO. 11) (e.g. claim 8), Dirks et al., teach that the sequence of SEQ ID NO. 11, as an alkaline phosphtase and its use as a reporter gene was known at the time of filing and that using SEQ ID NO. 11 is a matter of design choice (Dirks et al., col 7, line 57 to col., 8, line 5, see also sequence search printout for alignment, attached). With regard to the claims being drawn to use of a heat-resistant secretory alkaline phosphatase (e.g. claim 6), the art teaches that heat-resistant secretory alkaline phosphatases were known at the time of filing and that it would have been design choice for an artisan to use a heat-resistant secretory alkaline phosphatase in assays that treat media with heat as a step before measuring alkaline phosphatase activity (Ciccarone et al., col. 76, 4th parag.).

Thus, the claims are obvious.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Art Unit 1632